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INVESTIGATIONS OF THE VALUE OF NITROBENZOL AS A PARASITICIDE WITH NOTES ON ITS USE IN COLLECTING EXTERNAL PARASITES

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Incident to the recent appearance of an article (Moore, 1916) recommending as a regular procedure the fumigation of animals with *nitrobenzol* for the control of their external parasites, a great deal of interest was aroused in the apparent possibilities offered by the use of this drug in various phases of parasitological work. A number of experiments, both field and laboratory, involving its use were initiated by the Department of Entomology of Cornell University.

At the outset it appeared to those more familiar with the chemical nature and toxic properties of nitrobenzol, that it would be highly desirable to do some definite experimental work to determine the physiological action of this drug on animals when administered by vapor inhalation. There are on record in the Index Medicus (see nitrobenzol, nitrobenzene, oil of mirbane, etc.) a great number of reports of fatal cases of nitrobenzol poisoning in man resulting either from the ingestion of the liquid or absorption through the skin. A few instances of poisoning by inhaling the vapor are also recorded. There have also been done a few careful experiments upon laboratory animals (Filehne, 1878) in which the drug was administered in the liquid form by introducing it into the stomach through a tube and by intravenous injections; and in these experiments symptoms of nitrobenzol poisoning with fatal terminations are described after the administration of even small doses. So far as can be determined, however, no satisfactory experiments are recorded in which the drug was administered by vapor inhalation.

In view of this situation, Dr. M. Dresbach and the writer undertook investigations to determine the action of nitrobenzol upon various animals when such animals were exposed to the vapor of this drug at various temperatures and for various periods of time. The experiments have now been in progress for more than a year and are being conducted at the physiological laboratory of the Cornell University Medical College. The facilities and resources of this laboratory have been placed freely at our disposal. We have also received material assistance and valuable advice from members of the staffs of the departments of entomology, sanitary chemistry, physical chemistry and histology.

An attempt was made to simulate as far as possible the conditions recommended for the "fumigation of animals to destroy their external parasites." However, the necessity of reducing to a minimum all possible interfering factors, such as impurities in the nitrobenzol, excess of carbonic acid, excess of moisture, and variations in temperature was early recognized. Practically pure nitrobenzol was obtained by redistilling the commercial liquid until a product was obtained which proved experimentally to have a boiling point of 210.9° C. and a freezing point of 5.7° C., the boiling point and freezing point, respectively, of nitrobenzol (Landolt and Börnstein, 1912). Provisions were made in the construction of the apparatus for controlling the other possible interfering factors mentioned.

A detailed description of all the apparatus used will appear in a more technical paper dealing with this subject. In brief, the principal parts of the apparatus were as follows: A paraffin-lined metal tank of 40 cubic feet capacity, so constructed that it could be hermetically sealed with paraffin * and provided with glass windows in top and side through which observations of the temperature of the tank and the animal's condition could be made. In the center of the tank was firmly suspended a wire cage which served to protect the following: A triangular piece of linen, one end of which dipped into a container of nitrobenzol; a thermometer, and a small fan which was kept revolving at a rate sufficient to insure a homogeneous mixture of the air and other gases within the tank. A removable false bottom of wire netting served to keep the animal from contact with its excretions.

The procedure in any single experiment was a follows: The tank was freed from moisture, sufficiently for all practical purposes, by allowing plates of concentrated sulphuric acid to stand in it for a day or so, the tank being sealed. The sulphuric acid was then removed, nitrobenzol introduced into the container, the tank sealed again, the fan started, and a constant temperature maintained. After sufficient time had elapsed to insure complete saturation with nitrobenzol (this was shown experimentally to require several hours), the animal was quickly introduced, the tank sealed, and air saturated with nitrobenzol passed into the tank at a rate sufficient to insure aeration. An outlet was provided so that the air in the tank remained at atmospheric pressure. Observations were recorded as a rule every fifteen minutes.

The results of these experiments, obtained from observations made on a large number of dogs, cats, rabbits, rats, mice, guinea-pigs,

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* Paraffin was found to be the best substance for this purpose since it is neither attacked by nor permeable to nitrobenzol.

chickens, pigeons, and frogs, are being compiled for publication in a more extensive paper; but it may not be out of place here to state that in all of the cases observed nitrobenzol has a serious poisonous action when administered by vapor inhalation. The intensity of its action, the type of symptoms produced, and the time elapsing from the moment of fumigation to the first onset of the symptoms vary greatly with different species of animals and even with animals of the same species. The dominant symptoms in all animals seem to be profuse salivation (in dogs, cats, etc., vomiting), diarrhoea, loss of coordination of the voluntary muscles, particularly those of the extremities, and a general loss of muscular tonus. In dogs, guinea-pigs, and poultry muscular tremors were observed. There were also generally present long periods of clonic convulsions ending in tonic convulsions involving the whole body and followed by periods of depression. In rabbits, cats, and rats, depression seemed to be the dominant symptom; while in frogs, depression alone was observed. "In dogs the first symptom shown is vomiting. This is soon followed by loss of muscular coordination. The hind legs are the first usually to be affected; then follow the fore leg muscles, and then those of the neck, jaw, and trunk." (Dresbach and Chandler, 1917.) The animal may recover after about one week,* or may die as a result of respiratory failure following one of the convulsions.

The symptoms of nitrobenzol poisoning may make their appearance during the course of the fumigation, immediately following it, or not until after several days. In dogs four days, and in chickens six days have elapsed between the time of exposure to the vapor and the onset of the symptoms.†

The action of nitrobenzol upon the tissues of animals poisoned by inhaling the vapor of this drug was studied by histological methods. It is interesting to observe that sections through the cerebellum of dogs thus poisoned (fixed in 10 per cent. formalin in saturated aqueous solution of corrosive sublimate and stained by Nissl's method) show degenerative changes in Purkinje's cells, while no changes in any of the other cells of the entire central nervous system have been detected. A description of these changes with a discussion as to their significance will be presented in another paper.

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* In most of the cases observed the recovery has been complete. Two cases are under observation, however, in which there appear to be permanent cerebellar lesions.

† The apparent degrees of resistance and of susceptibility to the action of nitrobenzol evidenced in animals, even in those of the same species, are extremely interesting. In one experiment three kittens, all of the same litter, were simultaneously fumigated at a temperature of 22° C. for a period of three hours. Two hours after the experiment was begun one of the kittens died. The other two were removed from the tank at the end of three hours and were apparently unharmed, except that digestive functions had been retarded, and never developed any symptoms of nitrobenzol poisoning afterwards. In another experiment, two chickens were fumigated at 23 C. for eight hours. One of them (♂), died shortly after being removed from the tank, while the other (♀), developed symptoms of poisoning only after about six days and the symptoms were then but slight.

The effects of nitrobenzol upon insects, especially fleas and biting lice, parasitic on the animals under observation were studied in connection with all of these experiments. The toxic action of this drug appears to run a more rapid course and to be more intense in the case of the insects observed than in the case of mammals and birds. Beginning shortly after the host was first exposed to the fumes, fleas could be detected crawling excitedly in and out through the hairs, migrating towards the anterior end of the host, apparently as the result of efforts to penetrate more deeply into the hair. In about one-half hour after an experiment was begun it was not an uncommon sight to see the nose of a dog or cat literally swarming with fleas. At 23° C. the activities of the fleas continue for about an hour, when the fleas become stupefied and are easily shaken off by the host. If removed from the vapor after an exposure of one and one-half hours, both the fleas and biting lice of dogs are apparently dead; but while a few of them do not recover, a large percentage of them recover within a short time; in fact, in all cases where conditions of exposure were milder than those corresponding to 26° C. for a period of six hours, a large percentage of both fleas and lice recovered. Likewise, a large percentage of the biting lice of poultry were found to recover after any exposure milder than that corresponding to 27° C. for a period of eight hours. On the other hand, in one experiment an exposure at 25° C. for a period of three hours was sufficient to cause the death of a dog, in another experiment an exposure of five hours at 22° C. caused the death of a dog, while in still another experiment a dog was exposed to the vapor at 20° C. for a period of ten hours and developed no symptoms of nitrobenzol poisoning at all.

In view of the fact that it is impossible to predict just what effect any given condition of exposure to the vapor of nitrobenzol will have on an animal, and the fact that it appears to be impossible to kill either fleas or biting lice by any condition of exposure under that corresponding to 26° C.* for six hours, it is clearly evident that this drug cannot be used with any degree of safety in the "fumigation of animals to destroy their external parasites."† However, since it seems hardly

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[*] It has been suggested that while these insects recover after being removed from the vapor, they may eventually succumb to the action of the drug. Subsequent fumigations of the same animal have failed to prove this to be the case; however, much work is yet needed to be done on this score.

[†] The action of nitrobenzol upon internal parasites, particularly those inhabiting the blood, is at present being investigated .

probable that one hour's exposure to the vapor of nitrobenzol at temperatures between 20° C. and 25° C. will affect seriously any of the domesticated animals, while fleas and biting lice become stupified after an hour's exposure at the same temperatures and are shaken off by the host in great quantities, it is quite possible that nitrobenzol fumigation may be used to good advantage in collecting specimens of external parasites. The following instances of its use for this purpose may be of interest:

A hen was fumigated at 25° C. for one hour. The hen was apparently unharmed and there were recovered from a sheet of paper previously placed in the bottom of the box more than two hundred specimens of external parasites. The fumigation was repeated on the following day and more than one hundred additional specimens were recovered, making a total of three hundred twenty-six specimens recovered. There were represented in this collection five genera and eight species as follows:

Specimen	Number taken
Goniocotes hologaster	63
Goniocotes gigas	4
Lipeurus heterographus	11
Lipeurus variabilis	2
Menopon pallidum	228
Menopon biseriatum	13
Dermanyssus gallinae	3
Echidnophaga gallinaceus	2
Total	326

In another experiment a hen was fumigated at 26° C. for one and one-half hours. The hen was unharmed and there were recovered more than five hundred specimens of biting lice. Among these were eleven specimens of *Goniocotes gigas*, a species which has been rarely collected in the vicinity of Ithaca.

A young kitten was combed with a fine-toothed comb for the purpose of collecting fleas, but not more than two fleas could be discovered. The kitten was then fumigated at 20° C. for a period of one and one-half hours. In about one-half hour after the experiment was begun the animal's nose was black with highly excited fleas. One-half hour later, the fleas were lying stupefied on the paper in the bottom of the tank. There were recovered eighty-nine specimens of *Ctenocephalus felis* and two specimens of *Trichodectes subrostratus*.

A dog was fumigated at 23° C. for about an hour, and there were recovered a number of *Ctenocephalus*, a great quantity of *Trichodectes latus*, and two specimens of *Haematopinus piliferus*.

In the use of nitrobenzol fumigation for collecting purposes two advantages stand out: (1) Since the parasites become stupefied and are readily shaken off by the host on a piece of white paper placed in the bottom of the box, great quantities of different species of external parasites may be collected with scarcely any trouble at all; (2) since the parasites are only stupefied and not dead, they may be revived and used for experimental purposes or killed by any method desired.

In the practical use of nitrobenzol fumigation in collecting external parasites the apparatus need not, of course, be so extensive as in experiments to determine the action of this drug on animals, and can be constructed at small cost by any laboratory. It should consist of a wooden or metal box provided with a tightly fitting lid. The size of the box should be determined by the size of the animal to be fumigated (for dogs, cats, and other small animals one of 20 cubic feet capacity will be sufficiently large). The box should be coated inside with paraffin to prevent rust in case metal is used, or to prevent absorption of moisture by the wood in case wood is used. It should have a false removable bottom of wire netting, and should contain a small wire cage which will serve to protect a container for nitrobenzol and the cloth (a triangular piece of cheese-cloth with a 6-inch base will serve) from which the nitrobenzol is evaporated.

The procedure is likewise simple. Preparatory to the fumigation of an animal, the bottom of the box should be covered with clean white paper and the false bottom placed upon this. Nitrobenzol (the commercial product will serve) is then introduced into the container and the box closed. After two or three hours have elapsed, the lid should be partly removed, the animal quickly introduced and the box closed again. After the animal has been exposed to the vapor for from one to one and one-half hours, the box should be opened and the insects, which will be found on the white paper, collected at once and placed in a warm, airy place, in order to insure the recovery of a maximum number.

Operators should be cautioned not to fumigate an animal at a temperature higher than 25° C. or for a longer period than one and one-half hours.

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